Structural models of shikimate pathway enzymes

Walter F. de Azevedo Jr.
UNESP-S. J. do Rio Preto

The shikimate pathway is an attractive target for the development of herbicides and antimicrobial agents because it is essential in algae, higher plants, bacteria and fungi, but absent from mammals. The first step in the shikimate pathway is the condensation of phosphoenolpyruvate (PEP) and D-erythrose 4-phosphate (E4P) forming 3-deoxy-D-arabino-heptulosonate 7-phosphate (DAHP) catalyzed by DAHP synthase (DAHPS; EC 4.1.2.15). The second reaction is the elimination of phosphate from DAHP to generate 3-dehydroquinate (DHQ), which is catalyzed by DHQ synthase (DHQS; EC 4.6.1.3). In the third enzyme-catalyzed reaction, DHQ is dehydrated to 3-dehydroshikimate (DHS) by 3-dehydroquinate dehydratase (DHQ dehydratase; EC 4.2.1.10). The fourth is the reduction of 3-dehydroshikimate to shikimate catalyzed by shikimate dehydrogenase (SHK dehydrogenase; EC 1.1.1.25). Shikimate kinase (SK; EC 2.7.1.71), the fifth enzyme of the pathway, catalyzes a phosphate transfer from ATP to the carbon-3 hydroxyl group of shikimate forming shikimate 3-phosphate (S3P). The sixth reaction is an unusual transfer of an enolpyruvyl moiety from phosphoenolpyruvate (PEP) to the 5-hydroxyl group of S3P with the elimination of inorganic phosphate forming 5-enolpyruvylshikimate 3-phosphate (EPSP) catalyzed EPSP synthase (*aroA*-encoded EPSPS; EC 2.5.1.19). The final step in the main trunk of the shikimate pathway is the *trans*-1,4 elimination of phosphate from EPSP to yield chorismate catalyzed by chorismate synthase (CS; EC 4.6.1.4). Here we report structural studies using bioinformatics and crystallography for these seven enzymes identified in the *Mycobacterium tuberculosis* genome (www.biocristalografia.df.ibilce.unesp.br). Structural models for these enzymes will provide models for inhibitor design, which may generate a new generation of drugs against tuberculosis